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| EXAMINER | |
|---|---|
| ROONEY, NORA MAUREEN | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/038,509 | SMITH ET AL. | |
| | Examiner | Art Unit | |
| | NORA M. ROONEY | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/04/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. It is noted that an Action examining a method of detecting Graves disease in a patient comprising obtaining a biological sample from the patient and measuring the binding of disease specific IgG with IGF-1 relative to a control wherein an elevated level of IgG IgF-1 binding relative to the control indicates Graves disease was mailed on 04/04/2007. Applicant filed a response on 10/03/2007 changing the invention to recite examining a method of detecting Graves disease in a patient comprising obtaining a biological sample from the patient and measuring the binding of disease specific IgG with IGF-1 receptor relative to a control wherein an elevated level of IgG IgF-1 binding relative to the control indicates Graves disease. The Examiner mailed a non-responsive amendment letter on 10/29/2007 to Applicant informing them that they had changed their elected invention. Applicant responded on 01/28/2008 saying "The claims always had the proper abbreviation, i.e. IGF-1 R, and merely omitted the term "receptor" had merely been accidentally omitted." The Examiner sent another non-responsive amendment letter on 03/05/2008 informing Applicant that, contrary to their assertion, the claims had never been directed to a method of detecting Graves disease in a patient comprising obtaining a biological sample from the patient and measuring the binding of disease specific IgG with IGF-1 receptor relative to a control wherein an elevated level of IgG IgF-1 binding relative to the control indicates Graves disease. Applicant's responded on 03/17/2008 saying "Applicants incorrectly stated in their previous response that the claims always had the proper abbreviation, i.e. IGF-1 R, and merely omitted the term "receptor." Applicants apologize for this error and respectfully request entry of the above amendment, which Applicants' response filed October 3, 2007, had not properly presented by underlining the added abbreviation. However, Applicants respectfully

request that the Examiner continue examination of the corrected claims." Upon receiving the reply, the Examiner phoned Applicant's attorney Astrid Spain who acknowledged that the claims now recite a different invention than that which had previously been examined. Ms. Spain requested that the Examiner examine the amended claims as a courtesy since the error had been due to prior counsel and had gone unnoticed. The Examiner contacted Christopher Low in Quality Assurance and her SPE, Eileen O'Hara who authorized the Examiner to continue examination on the amended claims with a Final Rejection as set forth below.

2. Claims 1 and 3-11 are currently pending and under consideration as they read on a method of detecting Graves disease in a patient comprising obtaining a biological sample from the patient and measuring the binding of disease specific IgG with IGF-1 receptor relative to a control wherein an elevated level of IgG IgF-1 binding relative to the control indicates Graves disease.

3. Applicant's IDS document filed 04/04/2008 is acknowledged.

***Claim Objections***

4. Claim10 is objected to because of the following informalities: The word 'RANES' in claim 10, lines 6 should be changed to 'RANTES.' Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1 and 3-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites 'obtaining a biological sample' comprising fibroblasts from a patient, but it does not recite the source disease specific IgG. Claims 3-6 require T cells to perform the methods, but the source of the T cells is unclear.

7. Claims 1, 3-5 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. Claims 1, 3-5 and 7-8 do not recite activation or measurement contact steps. It is unclear how the methods are performed.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1 and 3-11 *are* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of detecting Graves' disease in a human patient comprising (a) obtaining a orbital or skin sample comprising fibroblasts from the patient, and (b) detecting in said orbital or skin sample the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein an increase in IgG-activated fibroblasts compared to the control indicates Graves' disease and wherein fibroblast activation is determined by measuring IL-16, RANTES or T cell migration; a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for IL-16 (c) detecting the level of IL-16 released by said fibroblasts relative to a control, wherein an elevated level of IL-16 detects the presence of antibody-activated fibroblasts; a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for RANTES; (c) detecting the level of RANTES released by said fibroblasts relative to a control, wherein an elevated level of RANES detects the presence of antibody-activated fibroblasts; a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with antibodies specific for IL-16 and RANTES; (c) detecting the levels of IL-16 and RANTES released by said fibroblasts relative to a control, wherein an elevated level. both IL-16 and RANTES detects the presence of antibody-activated fibroblasts. The specification does not provide reasonable enablement for : a method of detecting Graves' disease in a patient comprising (a) obtaining **a biological sample**

**comprising fibroblasts** from the patient, and (b) detecting in said biological sample the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control **wherein presence of IgG-activated fibroblasts compared to the control indicates Graves' disease** of claim 1; wherein the detecting is accomplished by measuring the level of **a chemical marker** expressed by said IgG-activated fibroblasts in said **biological sample**, wherein an elevated level of **the marker** compared to the control indicates presence of said IgG-activated fibroblasts of claim 3; wherein the marker is RANTES of claim 4; wherein the marker is IL- 16 of claim 5; wherein the detecting is accomplished by exposing T-cells to **said biological sample** comprising fibroblasts and measuring T-cell migration toward said fibroblasts, wherein an increase in the migration of said fibroblasts relative to the control indicates presence of said IgG-activated fibroblasts of claim 6; wherein the patient is human of claim 7; wherein the **biological sample** is selected from a group consisting of: **blood, urine, synovial fluid, ascites and tissues** of claim 8; A method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining **a biological sample** comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for IL-16 (c) detecting the level of IL-16 released by said fibroblasts relative to a control, wherein an elevated level of IL-16 detects the presence of antibody-activated fibroblasts of claim 9; A method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining **a biological sample** comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for RANTES; (c) detecting the level of RANTES released by said fibroblasts relative to a control, wherein an elevated level of RANES detects the presence of antibody-activated fibroblasts of claim 10; A method of detecting the presence of antibody-activated

fibroblasts, said method comprising (a) obtaining **a biological sample** comprising fibroblasts from the patient; (b) contacting said sample with antibodies specific for IL-16 and RANTES; (c) detecting the levels of IL-16 and RANTES released by said fibroblasts relative to a control, wherein an elevated level of both IL-16 and RANTES detects the presence of antibody-activated fibroblasts of claim 11. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

The specification discloses a method of detecting Graves disease or rheumatoid arthritis in a human patient comprising contacting an antibody sample with a fibroblast sample from the same patient and measuring the IL-16 and/or RANTES levels that are induced by the diseas-specific IgG activation of the IGF-1R on the fibroblast, whereby increased expression of either cytokine is associated with the presence of disease specific IgG and is an indicator of disease;

and a method of detecting Graves disease or rheumatoid arthritis in a human patient comprising: contacting an antibody sample with a fibroblast sample from the same patient; exposing a NWNA-T cell to the activated fibroblast using a Boyden chamber; measuring the T cell migration toward the activated fibroblast, and determining that positive T cell migration indicates IL-16 and/or RANTES expression in disease-specific IgG-activated fibroblasts through their IGF-1R, whereby increased expression of either cytokine is associated with the presence of disease specific IgG.

The term 'biological sample' in claim 1 encompasses any biological sample from any source, including sources that do not contain fibroblasts such as urine which is recited in claim 8. The art is highly unpredictable with regard obtaining fibroblasts from any fluid or tissue biological sample source.

The specification does not disclose a method of measuring any "chemical marker" expressed by fibroblasts to detect IgG-activated fibroblasts. The specification discloses only the measurement of RANTES and IL-16 as chemical markers of fibroblast activation. The term "chemical marker" encompasses a broad genus of indicators of fibroblast activation that don't necessarily have anything to do with Graves Disease such as increased expression of surface molecules or other normal cellular indicators of growth and differentiation.

The specification does not adequately disclose a method "wherein presence of IgG-activated fibroblasts compared to the control indicates Graves' disease" because this recitation

encompasses both positive and negative measurements. The specification discloses wherein an increase of IgG-activated fibroblasts compared to the control indicates Graves' disease.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 1 and 3-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method of detecting Graves' disease in a human patient comprising (a) obtaining a orbital or skin sample comprising fibroblasts from the patient, and (b) detecting in said orbital or skin sample the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein an increase in IgG-activated fibroblasts compared to the control indicates Graves' disease and wherein fibroblast activation is determined by measuring IL-16, RANTES or T cell migration; a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for IL-16 (c) detecting the level of IL-16 released by said fibroblasts relative to a

control, wherein an elevated level of IL-16 detects the presence of antibody-activated fibroblasts; a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for RANTES; (c) detecting the level of RANTES released by said fibroblasts relative to a control, wherein an elevated level of RANES detects the presence of antibody-activated fibroblasts; a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining an orbital or skin sample comprising fibroblasts from the patient; (b) contacting said sample with antibodies specific for IL-16 and RANTES; (c) detecting the levels of IL-16 and RANTES released by said fibroblasts relative to a control, wherein an elevated level. both IL-16 and RANTES detects the presence of antibody-activated fibroblasts

Applicant is not in possession of: a method of detecting Graves' disease in a patient comprising (a) obtaining **a biological sample comprising fibroblasts** from the patient, and (b) detecting in said biological sample the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein presence of IgG-activated fibroblasts compared to the control indicates Graves' disease of claim 1; wherein the detecting is accomplished by measuring the level of **a chemical marker** expressed by said IgG-activated fibroblasts in said **biological sample**, wherein an elevated level of **the marker** compared to the control indicates presence of said IgG-activated fibroblasts of claim 3; wherein the marker is RANTES of claim 4; wherein the marker is IL- 16 of claim 5; wherein the detecting is accomplished by exposing T-cells to **said biological sample** comprising fibroblasts and

measuring T-cell migration toward said fibroblasts, wherein an increase in the migration of said fibroblasts relative to the control indicates presence of said IgG-activated fibroblasts of claim 6; wherein the patient is human of claim 7; wherein the **biological sample** is selected from a group consisting of: **blood, urine, synovial fluid, ascites and tissues** of claim 8; A method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining **a biological sample** comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for IL-16 (c) detecting the level of IL-16 released by said fibroblasts relative to a control, wherein an elevated level of IL-16 detects the presence of antibody-activated fibroblasts of claim 9; A method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining **a biological sample** comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for RANTES; (c) detecting the level of RANTES released by said fibroblasts relative to a control, wherein an elevated level of RANES detects the presence of antibody-activated fibroblasts of claim 10; A method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining **a biological sample** comprising fibroblasts from the patient; (b) contacting said sample with antibodies specific for IL-16 and RANTES; (c) detecting the levels of IL-16 and RANTES released by said fibroblasts relative to a control, wherein an elevated level of both IL-16 and RANTES detects the presence of antibody-activated fibroblasts of claim 11

The specification has not adequately described the term 'biological sample' as it encompasses any biological sample from any source, including sources that do not contain fibroblasts such as urine which is recited in claim 8.

The specification does not describe a method of measuring any "chemical marker" expressed by fibroblasts to detect IgG-activated fibroblasts. The specification discloses only the measurement of RANTES and IL-16 as chemical markers of fibroblast activation. The term "chemical marker" encompasses a broad genus of indicators of fibroblast activation that don't necessarily have anything to do with Graves Disease such as increased expression of surface molecules or other normal cellular indicators of growth and differentiation. The specification has not adequately described the genus of all chemical markers for use in the claimed invention.

Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Kendall-Taylor et al. (PTO-892; Reference U).

Kendall-Taylor et al. teaches a method of detecting Graves' disease in a human patient comprising (a) obtaining a biological sample comprising fibroblasts (extraocular myoblasts at least 80% free of fibroblasts) from the patient, and (b) detecting in said biological sample the

activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein presence of IgG-activated fibroblasts compared to the control indicates Graves' disease; wherein the detecting is accomplished by measuring the level of a chemical marker (IGF-1) expressed by said IgG-activated fibroblasts in said biological sample (extraocular myoblasts at least 80% free of fibroblasts), wherein an elevated level of the marker (IGF-1) compared to the control indicates presence of said IgG-activated fibroblasts (In particular, abstract).

The reference teachings anticipate the claimed invention.

13. Claims 1, 3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Weightmann et al. (PTO-892; Reference V).

Weightmann et al. teaches a method of detecting Graves' disease in a human patient comprising (a) obtaining a biological sample comprising fibroblasts (3T3 cell line, tissue) from the patient (mouse), and (b) detecting in said biological sample (3T3 cell line) the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein presence of IgG-activated fibroblasts compared to the control indicates Graves' disease in the human patient (IgG donor) ; wherein the detecting is accomplished by measuring the level of a chemical marker (presence of 135kDa band) expressed by said IgG-activated fibroblasts in said biological sample (3T3 cell line, tissue), wherein an elevated level of the marker (presence

of 135kDa band) compared to the control indicates presence of said IgG-activated fibroblasts (In particular, abstract)

The reference teachings anticipate the claimed invention.

14. Claims 1, 3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Rotella et al. (IDS filed 11/04/2002).

Rotella et al. teaches a method of detecting Graves' disease in a human patient comprising (a) obtaining a skin sample comprising fibroblasts from the patient, and (b) detecting in said biological sample the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein presence of IgG-activated fibroblasts compared to the control indicates Graves' disease; wherein the detecting is accomplished by measuring the level of a chemical marker (collagen) expressed by said IgG-activated fibroblasts in said skin sample wherein an elevated level of the marker (collagen) compared to the control indicates presence of said IgG-activated fibroblasts (In particular, abstract, 'Cell Culture' section, last paragraph of page 363 to 'Discussion' section).

The reference teachings anticipate the claimed invention.

15. Claims 1, 3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Perros et al. et al. (IDS filed on 04/04/2008).

Perros et al. teaches a method of detecting Graves' disease in a human patient comprising (a) obtaining an orbital fibroblast sample from the patient, and (b) detecting in said biological sample the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein presence of IgG-activated fibroblasts compared to the control indicates Graves' disease; wherein the detecting is accomplished by measuring the level of a chemical marker (ICAM-1 and HSP72) expressed by said IgG-activated fibroblasts in said skin sample wherein an elevated level of the marker (ICAM-1 and HSP72) compared to the control indicates presence of said IgG-activated fibroblasts (In particular, page 121, 'fibroblast antibodies' section).

The reference teachings anticipate the claimed invention.

***Claim Rejections - 35 USC § 103***

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1 and 3-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kendall-Taylor et al.; Weightmann et al.; Perros et al.; or Rotella et al. each in view of Sciaky et al. (IDS filed on 11/04/2002) and Lim et al..(IDS filed on 11/04/2002).

Kendall-Taylor et al., Weightmann et al.; Perros et al.; and Rotella et al. have all been discussed *supra*.

The claimed invention differs from the prior art in the recitation of "wherein the marker is RANTES" of claim 4; "wherein the marker is IL- 16" of claim 5; "wherein the detecting is accomplished by exposing T-cells to said biological sample comprising fibroblasts and measuring T-cell migration toward said fibroblasts, wherein an increase in the migration of said fibroblasts relative to the control indicates presence of said IgG-activated fibroblasts" of claim 6; "a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining a biological sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for IL-16 (c) detecting the level of IL-16 released by said fibroblasts relative to a control, wherein an elevated level of IL-16 detects the presence of antibody-activated fibroblasts" of claim 9; "a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining a biological sample comprising fibroblasts from the patient; (b) contacting said sample with an antibody specific for RANTES; (c) detecting the level of RANTES released by said fibroblasts relative to a control, wherein an elevated level of RANES detects the presence of antibody-activated fibroblasts" of claim 10; and "a method of detecting the presence of antibody-activated fibroblasts, said method comprising (a) obtaining a biological sample comprising fibroblasts from the patient; (b) contacting said sample with antibodies specific for IL-16 and RANTES; (c) detecting the levels of IL-16 and RANTES released by said fibroblasts relative to a control, wherein an elevated level of both IL-16 and RANTES detects the presence of antibody-activated fibroblasts" of claim 11.

Sciaky et al. teaches that human fibroblasts express chemotactic cytokines IL-16 and RANTES upon activation which recruits T cells to the site of inflammation (In particular, whole document).

Lim et al. teaches that IL-16 and RANTES are chemoattractants for T cells and chemotaxis of T cells can be measured as an indication of the presence of IL-16 and RANTES (In particular, abstract, 'Lymphocyte Chemotaxis' section).

It would have been obvious to one of ordinary skill in the art at the time of invention to measure IL-6 and RANTES produced by fibroblasts as an additional indicator of fibroblast activation induced by IgG from Graves patients because Kendall-Taylor et al., Weightmann et al.; Perros et al.; and Rotella et al. are directed to measuring the activation of fibroblasts in response to IgG from Graves Disease patients. In addition to the activation markers measured in each of the Kendall-Taylor et al., Weightmann et al.; Perros et al., and Rotella et al., it would have been obvious to measure Il-16 and RANTES because Sciaky et al. teaches that chemotactic cytokines IL-16 and RANTES are expressed upon activation. It would have been obvious from the teachings of Lin et al. to detect IL-16 and RANTES expression by measuring T cell migration.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the

invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 22, 2008
Nora M. Rooney, M.S., J.D.
Patent Examiner
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/Maher M. Haddad/
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Art Unit 1644